EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	4594	dipyridamole	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/02/12 13:57
S2	29064	acetylsalicylic or aspirin or acetylsalicylate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/02/12 13:58
S3	2673	S1 and S2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/02/12 13:59
S4	912	telmisartan	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/02/12 13:59
S5	259	S3 and S4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/02/12 14:03
S6	475	S1.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/02/12 14:03
S7	2405	S2.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/02/12 14:03

EAST Search History

S8	200	S4.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/02/12 14:04
S9	25	S6 and S7 and S8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/02/12 14:17
S10	0	("10770971").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2007/02/12 14:17
S11	1	"10770971"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/02/12 14:17
S12	3	("3317279").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2007/02/12 16:49
S13	0	WO200130353	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/02/12 16:50
S14	1	"200130353"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/02/12 16:50

EAST Search History

S15	2	"20040214802"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 11:05
S16	2	"20070004687"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 11:44
S17	2	"20060241089"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 14:18
S18	3	("3317279").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2007/04/30 11:47
S19	0	wo200130353	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 14:18
S20	0	wo2001/30353	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 14:19
S21	0	wo01/30353	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 14:19

EAST Search History

S22	3	01/30353	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 14:19
S23	1	"200130353"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 14:23
S24	41	"0130353"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 14:23
S25	5	"2005038003"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 15:40
S26	3	"05038003"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 15:26
S27	0	"2005/038003"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 15:27
S28	1	"05/038003"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 15:27

EAST Search History

S29	2	"20050038003"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/04/30 15:40
S30	0	"10306179.7"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/06/20 18:07
S31	15	"10306179"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/06/20 18:58
S32	0	"200400214802".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/06/20 18:58
S33	2	"20040214802".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/06/20 18:58

21 June 2007 at 9:01 - ANSWER 1 OF 6

CAPLUS ©2007 ACS on STN
2007:522985-Full-text

Rationale, Design and Baseline Data of a Randomized, Double-Blind, Controlled Trial Comparing Two Antithrombotic Regimens (a Fixed-Dose Combination of Extended-Release Dipyridamole plus ASA with Clopidogrel) and Telmisartan versus Placebo in Patients with Strokes: The Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS)

Hans-Christoph Diener; Ralph Sacco; Salim Yusuf

National Stroke Research Institute, Melbourne, Australia

Journal

Cerebrovascular Diseases (Basel, Switzerland) (2007),
23(5-6), 368-380

Language

English

Abstract

Background: Individuals with **transient ischemic attack** and ischemic **stroke** have a high risk of recurrent **stroke** and death. While acetylsalicylic acid (ASA, aspirin) is proven and accepted as standard therapy in these patients, recent trials demonstrate that a combination of ASA and **dipyridamole** (DP) or clopidogrel may be superior to ASA. Blocking the renin-angiotensin system with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may also reduce recurrent **stroke.** The ongoing PRoFESS (Prevention Regimen for Effectively Avoiding Second **Strokes**) trial is designed to evaluate whether ASA + extended-release DP compared to clopidogrel, and whether **telmisartan** in addition to usual care in individuals after a **stroke,** will reduce the risk of further **strokes.** Methods: PRoFESS is a multicenter, randomized, double-blind trial involving 695 sites from 35 countries or regions. Patients ≥50 years presenting with an ischemic **stroke** <120 days who were stable were randomized. The primary outcome for the trial is recurrent **stroke,** using a time-to-event anal. The most important secondary outcome is the composite of **stroke,** myocardial infarction or vascular death. Other secondary outcomes include this composite + congestive heart failure, new-onset diabetes, other designated occlusive vascular events (pulmonary embolism, deep-vein thrombosis, peripheral arterial occlusion, **transient ischemic attack,** cerebral venous thrombosis or retinal vascular accident not classified as **stroke**), any death, **stroke** subtype by TOAST criteria and Mini Mental State Examination score. Safety is evaluated by assessing the risk of major hemorrhagic events. The comparison between ASA + DP and clopidogrel is based on an initial assessment of noninferiority, followed by evaluation of superiority, while for **telmisartan,** we will assess its superiority over placebo. Results: With over 20,000 patients randomized, and utilizing a 2 + 2 factorial design, PRoFESS is the largest **stroke** trial to investigate the prevention of recurrent **stroke.** The mean age was 66.1 ± 8.6 years, and 36.0% of the patients were females. The median time from qualifying event to randomization was 15 days with 39.9% of patients randomized within 10 days. According to the TOAST criteria, 28.5% of the **strokes** were due to large-vessel disease, 52.1% to small-vessel disease, 1.8% to cardioembolism, and 2.0% to other determined etiologies and 15.5% were of undetd. etiol. Conclusions: PRoFESS is the largest secondary **stroke** prevention trial to date and will directly compare two antiplatelet regimens as well as the benefit of **telmisartan** vs. placebo.

21 June 2007 at 9:01 - ANSWER 2 OF 6

CAPLUS ©2007 ACS on STN
2006:796115-Full-text

Combination pain medication comprises a combination of an NSAID and proton pump inhibitor

Patent Number US 2006177504 A1 10 August, 2006

USA

U.S. Pat. Appl. Publ., 4pp.

Abstract

This patent is an evolution of previous combination medication patents. Previous combination patents such as U.S. Pat. Number 6,613,354 which is a combination of an NSAID and proton pump inhibitor. Thus, the previous patents have covered gastrointestinal prophylaxis but none has covered both gastrointestinal and cardiovascular prophylaxis. This is likely because the cardiovascular side effects of NSAIDs were only recently discovered. This patent thus represents a leap in safety in a class of medication that is used by millions of Americans on a daily basis. This combination would thus decrease morbidity and mortality. An over the counter medication contains 200 mg ibuprofen per tablet and is supposed to be taken as four tablets four times daily as the maximum dose. Such tablet may contain 1.25 mg of omeprazole per tablet, addnl., this tablet could contain 2.5 mg of famotidine.

Language

English

Inventor(s)

Sundharadas, Renjit

Application Information

US 2006-349587 8 February, 2006

Priority Information

US 2005-651034P P 8 February, 2005
US 2005-703789P P 30 July, 2005

Patent Information

Number	Kind	Date	Application	Date
US 2006177504	A1	10 August, 2006	US 2006-349587	8 February, 2006

21 June 2007 at 9:01 - ANSWER 3 OF 6

CAPLUS ©2007 ACS on STN
2004:701942-Full-text

Use of dipyridamole in combination with acetylsalicylic acid and an angiotensin II antagonist for stroke prevention

Patent Number WO 2004071385 A2 26 August, 2004

Boehringer Ingelheim International GmbH, Germany; Boehringer Ingelheim Pharma GmbH & Co. Kg

PCT Int. Appl., 8 pp.

Abstract

This invention relates to a method of preventing **stroke** or reducing the risk of **stroke** in a patient in need thereof, especially in a patient at risk for a **stroke** or a secondary **stroke** , using **dipyridamole** in combination with acetylsalicylic acid (ASA) and an angiotensin II antagonist, corresponding pharmaceutical compns., and the use of **dipyridamole** for the manufacture of a corresponding pharmaceutical composition comprising a combination of **dipyridamole**, acetyl salicylic acid and an angiotensin II antagonist.

Language

English

Inventor(s)

Hilbrich, Lutz; Gilbert, James C.; Humphreys, Michael; Riedel, Axel

Application Information

WO 2004-EP1208 10 February, 2004

Priority Information

DE 2003-10306179 A 13 February, 2003
EP 2003-18212 A 8 August, 2003
WO 2004-EP1208 A 10 February, 2004

Patent Information

Number	Kind	Date	Application	Date
WO 2004071385	A2	26 August, 2004	WO 2004-EP1208	10 February, 2004
(1) WO 2004071385	A3	6 January, 2005		
DE 10306179	A1	26 August, 2004	DE 2003-10306179	13 February, 2003
AU 2004212305	A1	26 August, 2004	AU 2004-212305	10 February, 2004
CA 2515941	A1	26 August, 2004	CA 2004-2515941	10 February, 2004
(2) EP 1603573	A2	14 December, 2005	EP 2004-709596	10 February, 2004
BR 2004007457	A	31 January, 2006	BR 2004-7457	10 February, 2004
JP 2006517557	T	27 July, 2006	JP 2006-501788	10 February, 2004
US 2007004687	A1	4 January, 2007	US 2005-544239	2 August, 2005
IN 2005DN03517	A	5 January, 2007	IN 2005-DN3517	8 August, 2005
NO 2005004216	A	12 September, 2005	NO 2005-4216	12 September, 2005

(1) **W:** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO **RW:** BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
(2) **R:** AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

2004:695236-Full-text

Use of dipyridamole in combination with acetylsalicylic acid and an angiotensin II antagonist for stroke prophylaxis

Patent Number DE 10306179 A1 26 August, 2004

Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G., Germany

Ger. Offen., 4 pp.

Abstract

The invention provides a method for **stroke** prophylaxis or for the decrease of the **stroke** risk in an endangered patient, in particular in a patient with the risk of a **stroke** or a secondary **stroke.** The method uses **dipyridamole** in combination with acetylsalicylic acid and an angiotensin II antagonist, e.g. **telmisartan.** The invention also provides appropriate pharmaceutical compns., as well as the use of **dipyridamole** for the production of an appropriate pharmaceutical composition containing a combination of **dipyridamole**, acetylsalicylic acid, and an angiotensin II antagonist.

Language

German

Inventor(s)

Gilbert, James C.; Hilbrich, Lutz; Riedel, Axel; Humphreys, David Michael

Application Information

DE 2003-10306179 13 February, 2003

Priority Information

DE 2003-10306179 A 13 February, 2003
US 2003-447090P P 13 February, 2003
EP 2003-18212 A 8 August, 2003
US 2003-503179P P 16 September, 2003
US 2004-770971 B1 3 February, 2004
EP 2004-709596 A3 10 February, 2004
WO 2004-EP1208 A 10 February, 2004

Patent Information

Number	Kind	Date	Application	Date
DE 10306179	A1	26 August, 2004	DE 2003-10306179	13 February, 2003
JP 2005060359	A	10 March, 2005	JP 2003-325255	13 August, 2003
CA 2437709	A1	20 February, 2005	CA 2003-2437709	20 August, 2003
US 2004214802	A1	28 October, 2004	US 2004-770971	3 February, 2004
AU 2004212305	A1	26 August, 2004	AU 2004-212305	10 February, 2004
CA 2515941	A1	26 August, 2004	CA 2004-2515941	10 February, 2004
WO 2004071385	A2	26 August, 2004	WO 2004-EP1208	10 February, 2004
(1) WO 2004071385	A3	6 January, 2005		
(2) EP 1603573	A2	14 December, 2005	EP 2004-709596	10 February, 2004

BR 2004007457	A	31 January, 2006	BR 2004-7457	10 February, 2004
CN 1750830	A	22 March, 2006	CN 2004-80004107	10 February, 2004
JP 2006517557	T	27 July, 2006	JP 2006-501788	10 February, 2004
(3) EP 1733729	A1	20 December, 2006	EP 2006-121998	10 February, 2004
US 2007004687	A1	4 January, 2007	US 2005-544239	2 August, 2005
IN 2005DN03517	A	5 January, 2007	IN 2005-DN3517	8 August, 2005
NO 2005004216	A	12 September, 2005	NO 2005-4216	12 September, 2005
ZA 2005005956	A	29 March, 2006	ZA 2005-5956	9 February, 2006
US 2006241089	A1	26 October, 2006	US 2006-478184	29 June, 2006

(1) **W:** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO **RW:** BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
(2) **R:** AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
(3) **R:** AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PT, RO, SE, SI, SK, TR, LT, LV

21 June 2007 at 9:01 - ANSWER 5 OF 6

MEDLINE
2007280124-Full-text

Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS).

Diener Hans-Christoph; Sacco Ralph; Yusuf Salim

Department of Neurology, University Duisburg- EssenHufelandstrasse 55DE-45122 Essen, Germany. (Steering Committee; PRoFESS Study Group). h.diener@uni-essen.de

Journal

Cerebrovascular diseases (Basel, Switzerland), (2007) Vol. 23, No. 5-6, pp. 368-80. Electronic Publication: 2007-02-26.
Journal code: 9100851. ISSN: 1015-9770.

Language

English

Abstract

BACKGROUND: Individuals with **transient ischemic attack** and ischemic **stroke** have a high risk of recurrent **stroke** and

death. While acetylsalicylic acid (ASA, aspirin) is proven and accepted as standard therapy in these patients, recent trials demonstrate that a combination of ASA and **dipyridamole** (DP) or clopidogrel may be superior to ASA. Blocking the renin-angiotensin system with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may also reduce recurrent **stroke**. The ongoing PRoFESS (Prevention Regimen for Effectively Avoiding Second **Strokes**) trial is designed to evaluate whether ASA + extended-release DP compared to clopidogrel, and whether **telmisartan** in addition to usual care in individuals after a **stroke**, will reduce the risk of further **strokes**. METHODS: PRoFESS is a multicenter, randomized, double-blind trial involving 695 sites from 35 countries or regions. Patients > or = 50 years presenting with an ischemic **stroke** < 120 days who were stable were randomized. The primary outcome for the trial is recurrent **stroke**, using a time-to-event analysis. The most important secondary outcome is the composite of **stroke**, myocardial infarction or vascular death. Other secondary outcomes include this composite + congestive heart failure, new-onset diabetes, other designated occlusive vascular events (pulmonary embolism, deep-vein thrombosis, peripheral arterial occlusion, **transient ischemic attack**, cerebral venous thrombosis or retinal vascular accident not classified as **stroke**), any death, **stroke** subtype by TOAST criteria and Mini Mental State Examination score. Safety is evaluated by assessing the risk of major hemorrhagic events. The comparison between ASA + DP and clopidogrel is based on an initial assessment of noninferiority, followed by evaluation of superiority, while for **telmisartan**, we will assess its superiority over placebo. RESULTS: With over 20,000 patients randomized, and utilizing a 2 x 2 factorial design, PRoFESS is the largest **stroke** trial to investigate the prevention of recurrent **stroke**. The mean age was 66.1 +/- 8.6 years, and 36.0% of the patients were females. The median time from qualifying event to randomization was 15 days with 39.9% of patients randomized within 10 days. According to the TOAST criteria, 28.5% of the **strokes** were due to large-vessel disease, 52.1% to small-vessel disease, 1.8% to cardioembolism, and 2.0% to other determined etiologies and 15.5% were of undetermined etiology. CONCLUSIONS: PRoFESS is the largest secondary **stroke** prevention trial to date and will directly compare two antiplatelet regimens as well as the benefit of **telmisartan** versus placebo.

21 June 2007 at 9:01 - ANSWER 6 OF 6

MEDLINE
2003419797-Full-text

[Recurrence prophylaxis for stroke patients. Which platelet inhibitor combination protects best?]. Rezidivprophylaxe fur Schlaganfall-Patienten. Welche Plattchenhemmer-Kombination schutzt am besten?.

Anonymous

Journal

MMW Fortschritte der Medizin, (2003 Jul 24) Vol. 145, No. 29-30, pp. 63.
Journal code: 100893959. ISSN: 1438-3276.

Language

German

21 June 2007 at 9:01 - ANSWER 1 OF 11

CAPLUS ©2007 ACS on STN
2007:522985-Full-text

Rationale, Design and Baseline Data of a Randomized, Double-Blind, Controlled Trial Comparing Two Antithrombotic Regimens (a Fixed-Dose Combination of Extended-Release Dipyridamole plus ASA with Clopidogrel) and Telmisartan versus Placebo in Patients with Strokes: The Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS)

Hans-Christoph Diener; Ralph Sacco; Salim Yusuf

National Stroke Research Institute, Melbourne, Australia

Journal

Cerebrovascular Diseases (Basel, Switzerland) (2007),
23(5-6), 368-380

Language

English

Abstract

Background: Individuals with **transient ischemic attack** and ischemic **stroke** have a high risk of recurrent **stroke** and death. While **acetylsalicylic acid** (**ASA, aspirin**) is proven and accepted as standard therapy in these patients, recent trials demonstrate that a combination of ASA and dipyridamole (DP) or clopidogrel may be superior to **ASA.** Blocking the renin-angiotensin system with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may also reduce recurrent **stroke.** The ongoing PRoFESS (Prevention Regimen for Effectively Avoiding Second **Strokes**) trial is designed to evaluate whether ASA + extended-release DP compared to clopidogrel, and whether **telmisartan** in addition to usual care in individuals after a **stroke,** will reduce the risk of further **strokes.** Methods: PRoFESS is a multicenter, randomized, double-blind trial involving 695 sites from 35 countries or regions. Patients ≥50 years presenting with an ischemic **stroke** <120 days who were stable were randomized. The primary outcome for the trial is recurrent **stroke,** using a time-to-event anal. The most important secondary outcome is the composite of **stroke,** myocardial infarction or vascular death. Other secondary outcomes include this composite + congestive heart failure, new-onset diabetes, other designated occlusive vascular events (pulmonary embolism, deep-vein thrombosis, peripheral arterial occlusion, **transient ischemic attack,** cerebral venous thrombosis or retinal vascular accident not classified as **stroke**), any death, **stroke** subtype by TOAST criteria and Mini Mental State Examination score. Safety is evaluated by assessing the risk of major hemorrhagic events. The comparison between ASA + DP and clopidogrel is based on an initial assessment of noninferiority, followed by evaluation of superiority, while for **telmisartan,** we will assess its superiority over placebo. Results: With over 20,000 patients randomized, and utilizing a 2 + 2 factorial design, PRoFESS is the largest **stroke** trial to investigate the prevention of recurrent **stroke.** The mean age was 66.1 ± 8.6 years, and 36.0% of the patients were females. The median time from qualifying event to randomization was 15 days with 39.9% of patients randomized within 10 days. According to the TOAST criteria, 28.5% of the **strokes** were due to large-vessel disease, 52.1% to small-vessel disease, 1.8% to cardioembolism, and 2.0% to other determined etiologies and 15.5% were of undetd. etiol. Conclusions: PRoFESS is the largest secondary **stroke** prevention trial to date and will directly compare two antiplatelet regimens as well as the benefit of **telmisartan** vs. placebo.

21 June 2007 at 9:01 - ANSWER 2 OF 11

CAPLUS ©2007 ACS on STN
2006:1147258-Full-text

Preparation of multicyclic peptide derivatives as dipeptidyl peptidase-IV inhibitors

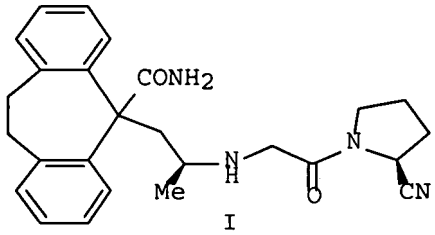
Patent Number WO 2006116157 A2 2 November, 2006

Alantos Pharmaceuticals, Inc., USA

PCT Int. Appl., 542pp.

Abstract

The invention relates generally to pyrrolidine and thiazolidine DPP-IV inhibitory compds. A-B-CO-D (A is a bicyclic or tricyclic ring system attached to B at carbon or nitrogen; B is a linking group such as an amino acid residue or fragment; D is a pyrrolidine or thiazolidine residue or derivative), including isomers and pharmaceutically-acceptable salts, for treatment of DPP-IV mediated diseases, in particular, type-2 diabetes. Thus, pyrrolidinecarbonitrile derivative I was prepared by reaction of 5-[(S)-2-aminopropyl]-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-carboxamide with N-glyoxyloyl-L-prolinecarbonitrile(prepns. given) and showed Ki < 6 nM for inhibition of DPP-IV.



I

Language

English

Inventor(s)

Kroth, Heiko; Feuerstein, Tim; Richter, Frank; Boer, Jurgen; Essers, Michael; Nolte, Bert; Schneider, Matthias; Hochguertel, Matthias; Frickel, Fritz-Frieder; Taveras, Arthur

Application Information

WO 2006-US15200 21 April, 2006

Priority Information

US 2005-674151P P 22 April, 2005

Patent Information

Number	Kind	Date	Application	Date
WO 2006116157	A2	2 November, 2006	WO 2006-US15200	21 April, 2006
WO 2006116157	A9	1 March, 2007		
(1) WO 2006116157	A3	19 April, 2007		
US 2006270701	A1	30 November, 2006	US 2006-409481	21 April, 2006

(1) **W:** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW **RW:** AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

21 June 2007 at 9:01 - ANSWER 3 OF 11

CAPLUS ©2007 ACS on STN
2006:796115-Full-text

Combination pain medication comprises a combination of an NSAID and proton pump inhibitor

Patent Number US 2006177504 A1 10 August, 2006

USA

U.S. Pat. Appl. Publ., 4pp.

Abstract

This patent is an evolution of previous combination medication patents. Previous combination patents such as U.S. Pat. Number 6,613,354 which is a combination of an NSAID and proton pump inhibitor. Thus, the previous patents have covered gastrointestinal prophylaxis but none has covered both gastrointestinal and cardiovascular prophylaxis. This is likely because the cardiovascular side effects of NSAIDs were only recently discovered. This patent thus represents a leap in safety in a class of medication that is used by millions of Americans on a daily basis. This combination would thus decrease morbidity and mortality. An over the counter medication contains 200 mg ibuprofen per tablet and is supposed to be taken as four tablets four times daily as the maximum dose. Such tablet may contain 1.25 mg of omeprazole per tablet, addnl., this tablet could contain 2.5 mg of famotidine.

Language

English

Inventor(s)

Sundharadas, Renjit

Application Information

US 2006-349587 8 February, 2006

Priority Information

US 2005-651034P P 8 February, 2005
US 2005-703789P P 30 July, 2005

Patent Information

Number	Kind	Date	Application	Date
US 2006177504	A1	10 August, 2006	US 2006-349587	8 February, 2006

21 June 2007 at 9:01 - ANSWER 4 OF 11

CAPLUS ©2007 ACS on STN
2005:472159-Full-text

Preparation of 5,7-diaminopyrazolo[4,3-d]pyrimidines with phosphodiesterase-5 (PDE5) inhibiting activity

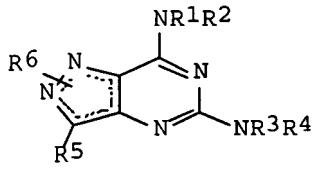
Patent Number WO 2005049616 A1 2 June, 2005

Pfizer Limited, UK; Pfizer Inc.

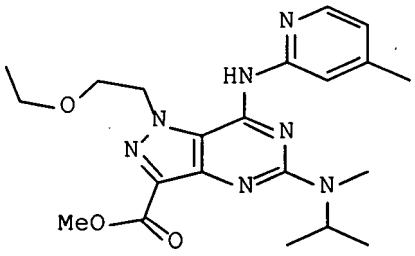
PCT Int. Appl., 282 pp.

Abstract

Title compds. [I; R1 = (substituted) cyclic group; R2 = H, alkyl; R3, R4 = (substituted) alkyl, alkenyl, alkynyl, cycloalkyl; R5 = YCO2R15, YR16; R6 = H, (substituted) alkyl, alkenyl, alkynyl, cycloalkyl, etc.; Y = bond, CH2OCH2, alkylene, cycloalkylene; R15 = H, (substituted) alkyl; R16 = tetrazolyl, trifluoromethyltriazolyl, methylsulfonyltriazolyl, etc.; dotted lines = double bonds to form an aromatic ring], were prepared Thus, title compound (II) (preparation given) inhibited PDE-5 with IC50 = 0.075 nM.



I



II

Language

English

Inventor(s)

Bell, Andrew Simon; Brown, David Graham; Dack, Kevin Neil; Fox, David Nathan Abraham; Marsh, Ian Roger; Morrell, Andrew Ian; Palmer, Michael John; Winslow, Carol Ann

Application Information

WO 2004-IB3747 12 November, 2004

Priority Information

GB 2003-27319 A 24 November, 2003
US 2004-535797P P 12 January, 2004
WO 2004-IB3747 W 12 November, 2004

Patent Information

Number	Kind	Date	Application	Date
WO 2005049616	A1	2 June, 2005	WO 2004-IB3747	12 November, 2004
(1) WO 2005049616	A8	1 June, 2006		
AU 2004290643	A1	2 June, 2005	AU 2004-290643	12 November, 2004
CA 2546987	A1	2 June, 2005	CA 2004-2546987	12 November, 2004
(2) EP 1689751	A1	16 August, 2006	EP 2004-798876	12 November, 2004
CN 1882591	A	20 December, 2006	CN 2004-80034570	12 November, 2004
BR 2004016869	A	27 March, 2007	BR 2004-16869	12 November, 2004
JP 2007512314	T	17 May, 2007	JP 2006-540647	12 November, 2004
NL 1027568	A1	26 May, 2005	NL 2004-1027568	23 November, 2004
NL 1027568	C2	30 November, 2005		
US 2005245544	A1	3 November, 2005	US 2004-997191	24 November, 2004

NO 2006002950	A	23 August, 2006	NO 2006-2950	23 June, 2006

(1) **W:** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW **RW:** BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
(2) **R:** AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR, IS, YU

CAPLUS ©2007 ACS on STN
2004:701942-Full-text

Use of dipyridamole in combination with acetylsalicylic acid and an angiotensin II antagonist for stroke prevention

Patent Number WO 2004071385 A2 26 August, 2004

Boehringer Ingelheim International GmbH, Germany; Boehringer Ingelheim Pharma GmbH & Co. Kg

PCT Int. Appl., 8 pp.

Abstract

This invention relates to a method of preventing **stroke** or reducing the risk of **stroke** in a patient in need thereof, especially in a patient at risk for a **stroke** or a secondary **stroke** , using dipyridamole in combination with **acetylsalicylic acid (ASA)** and an angiotensin II antagonist, corresponding pharmaceutical compns., and the use of dipyridamole for the manufacture of a corresponding pharmaceutical composition comprising a combination of dipyridamole, acetyl salicylic acid and an angiotensin II antagonist.

Language

English

Inventor(s)

Hilbrich, Lutz; Gilbert, James C.; Humphreys, Michael; Riedel, Axel

Application Information

WO 2004-EP1208 10 February, 2004

Priority Information

DE 2003-10306179 A 13 February, 2003
EP 2003-18212 A 8 August, 2003
WO 2004-EP1208 A 10 February, 2004

Patent Information

Number	Kind	Date	Application	Date
WO 2004071385	A2	26 August, 2004	WO 2004-EP1208	10 February, 2004

(1) WO 2004071385	A3	6 January, 2005		
DE 10306179	A1	26 August, 2004	DE 2003-10306179	13 February, 2003
AU 2004212305	A1	26 August, 2004	AU 2004-212305	10 February, 2004
CA 2515941	A1	26 August, 2004	CA 2004-2515941	10 February, 2004
(2) EP 1603573	A2	14 December, 2005	EP 2004-709596	10 February, 2004
BR 2004007457	A	31 January, 2006	BR 2004-7457	10 February, 2004
JP 2006517557	T	27 July, 2006	JP 2006-501788	10 February, 2004
US 2007004687	A1	4 January, 2007	US 2005-544239	2 August, 2005
IN 2005DN03517	A	5 January, 2007	IN 2005-DN3517	8 August, 2005
NO 2005004216	A	12 September, 2005	NO 2005-4216	12 September, 2005

(1) **W:** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO **RW:** BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
(2) **R:** AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

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2004:695236-Full-text

Use of dipyridamole in combination with acetylsalicylic acid and an angiotensin II antagonist for stroke prophylaxis

Patent Number DE 10306179 A1 26 August, 2004

Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G., Germany

Ger. Offen., 4 pp.

Abstract

The invention provides a method for **stroke** prophylaxis or for the decrease of the **stroke** risk in an endangered patient, in particular in a patient with the risk of a **stroke** or a secondary **stroke.** The method uses dipyridamole in combination with **acetylsalicylic acid** and an angiotensin II antagonist, e.g. **telmisartan.** The invention also provides appropriate pharmaceutical compns., as well as the use of dipyridamole for the production of an appropriate pharmaceutical composition containing a combination of dipyridamole, **acetylsalicylic acid,** and an angiotensin II antagonist.

Language

German

Inventor(s)

Gilbert, James C.; Hilbrich, Lutz; Riedel, Axel; Humphreys, David Michael

Application Information

DE 2003-10306179 13 February, 2003

Priority Information

DE 2003-10306179 A 13 February, 2003
US 2003-447090P P 13 February, 2003
EP 2003-18212 A 8 August, 2003
US 2003-503179P P 16 September, 2003
US 2004-770971 B1 3 February, 2004
EP 2004-709596 A3 10 February, 2004
WO 2004-EP1208 A 10 February, 2004

Patent Information

Number	Kind	Date	Application	Date
DE 10306179	A1	26 August, 2004	DE 2003-10306179	13 February, 2003
JP 2005060359	A	10 March, 2005	JP 2003-325255	13 August, 2003
CA 2437709	A1	20 February, 2005	CA 2003-2437709	20 August, 2003
US 2004214802	A1	28 October, 2004	US 2004-770971	3 February, 2004
AU 2004212305	A1	26 August, 2004	AU 2004-212305	10 February, 2004
CA 2515941	A1	26 August, 2004	CA 2004-2515941	10 February, 2004
WO 2004071385	A2	26 August, 2004	WO 2004-EP1208	10 February, 2004
(1) WO 2004071385	A3	6 January, 2005		
(2) EP 1603573	A2	14 December, 2005	EP 2004-709596	10 February, 2004
BR 2004007457	A	31 January, 2006	BR 2004-7457	10 February, 2004
CN 1750830	A	22 March, 2006	CN 2004-80004107	10 February, 2004
JP 2006517557	T	27 July, 2006	JP 2006-501788	10 February, 2004
(3) EP 1733729	A1	20 December, 2006	EP 2006-121998	10 February, 2004
US 2007004687	A1	4 January, 2007	US 2005-544239	2 August, 2005
IN 2005DN03517	A	5 January, 2007	IN 2005-DN3517	8 August, 2005
NO 2005004216	A	12 September, 2005	NO 2005-4216	12 September, 2005
ZA 2005005956	A	29 March, 2006	ZA 2005-5956	9 February, 2006
US 2006241089	A1	26 October, 2006	US 2006-478184	29 June, 2006

(1) **W:** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,

MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO **RW:** BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
(2) **R:** AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
(3) **R:** AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PT, RO, SE, SI, SK, TR, LT, LV

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2003:203196-Full-text

Treatment of patients at elevated cardiovascular risk with a combination of a cholesterol-lowering agent, an inhibitor of the renin-angiotensin system, and aspirin

Patent Number US 2003049314 A1 13 March, 2003

USA

U.S. Pat. Appl. Publ., 14 pp.

Abstract

Methods and compns. are provided for reducing the risk of cardiovascular events in individuals who are at elevated cardiovascular risk, including individuals who have systemic lupus erythematosus. The methods comprise administering a combination of: a cholesterol-lowering agent, such as an HMG CoA reductase inhibitor; an inhibitor of the renin-angiotensin system, such as an ACE inhibitor; **aspirin**; and optionally one or more of vitamin B6, vitamin B12, and folic acid. Pharmaceutical formulations combining all the active agents in unit-dose form for once-daily dosing are provided. Tablets containing pravastatin 40 mg, ramipril 10 mg, **aspirin** (in enteric coated granules) 81 mg, Vitamin B6 50 mg, Vitamin B12 1 mg, folic acid 3 mg, calcium carbonate 50 mg, magnesium oxide 25 mg, magnesium carbonate 25 mg, microcryst. cellulose 25 mg, lactose 25 mg, and magnesium stearate 1 mg are used to treat subjects at elevated cardiac risk.

Language

English

Inventor(s)

Liang, Matthew H.; Manson, Joann E.

Application Information

US 2001-942084 28 August, 2001

Priority Information

US 2001-942084 28 August, 2001

Patent Information

Number	Kind	Date	Application	Date
US 2003049314	A1	13 March, 2003	US 2001-942084	28 August, 2001
US 6576256	B2	10 June, 2003		

CAPLUS ©2007 ACS on STN
2001:167788-Full-text

Use of inhibitors of the renin-angiotensin system in the prevention of cardiovascular events

Patent Number WO 2001015674 A2 8 March, 2001

Aventis Pharma Deutschland G.m.b.H., Germany

PCT Int. Appl., 33 pp.

Abstract

The invention discloses the use of an inhibitor of the renin-angiotensin system, or a pharmaceutically acceptable derivative thereof, optionally together with an other antihypertensive, a cholesterol lowering agent, a diuretic, or **aspirin**, in the manufacture of a medicament for the prevention of cardiovascular events; a method of preventing cardiovascular events comprising administering to a patient in need of such prevention an effective amount of an inhibitor of the renin angiotensin system, or a pharmaceutically acceptable derivative thereof, optionally together with an other antihypertensive, a cholesterol lowering agent, a diuretic or **aspirin**; and a combination product containing an inhibitor of the renin-angiotensin system, or a pharmaceutically acceptable derivative thereof, and a cholesterol lowering agent.

Language

English

Inventor(s)

Schoelkens, Bernward; Bender, Norbert; Rangoonwala, Badrudin; Yusuf, Salim

Application Information

WO 2000-EP8461 30 August, 2000

Priority Information

US 1999-151436P P 30 August, 1999
AU 2000-76491 A3 30 August, 2000
CA 2000-2382549 A3 30 August, 2000
EP 2000-965906 A3 30 August, 2000
US 2000-651275 B1 30 August, 2000
WO 2000-EP8461 W 30 August, 2000
US 2003-694001 A3 28 October, 2003

Patent Information

Number	Kind	Date	Application	Date
WO 2001015674	A2	8 March, 2001	WO 2000-EP8461	30 August, 2000
(1) WO 2001015674	A3	28 March, 2002		
CA 2382549	A1	8 March, 2001	CA 2000-2382549	30 August, 2000
CA 2382549	C	15 March, 2005		
CA 2488370	A1	8 March, 2001	CA 2000-2488370	30 August, 2000

BR 2000013704	A	7 May, 2002	BR 2000-13704	30 August, 2000
EP 1216038	A2	26 June, 2002	EP 2000-965906	30 August, 2000
(2) EP 1216038	B1	7 September, 2005		
TR 200200515	T2	21 November, 2002	TR 2002-515	30 August, 2000
HU 200203326	A2	28 February, 2003	HU 2002-3326	30 August, 2000
EE 200200086	A	15 April, 2003	EE 2002-86	30 August, 2000
JP 2003527325	T	16 September, 2003	JP 2001-519888	30 August, 2000
NZ 517468	A	27 February, 2004	NZ 2000-517468	30 August, 2000
AT 303800	T	15 September, 2005	AT 2000-965906	30 August, 2000
(3) EP 1611886	A2	4 January, 2006	EP 2005-17162	30 August, 2000
ES 2246894	T3	1 March, 2006	ES 2000-965906	30 August, 2000
RU 2276997	C2	27 May, 2006	RU 2002-107985	30 August, 2000
BG 106360	A	31 October, 2002	BG 2002-106360	28 January, 2002
ZA 2002001470	A	21 August, 2003	ZA 2002-1470	21 February, 2002
NO 2002000978	A	18 April, 2002	NO 2002-978	27 February, 2002
HK 1048267	A1	8 December, 2006	HK 2003-100570	23 January, 2003
US 2004087645	A1	6 May, 2004	US 2003-694001	28 October, 2003
NZ 530702	A	29 July, 2005	NZ 2004-530702	20 January, 2004
US 2005101658	A1	12 May, 2005	US 2004-1028	2 December, 2004
AU 2005209687	A1	6 October, 2005	AU 2005-209687	13 September, 2005
US 2007021491	A1	25 January, 2007	US 2006-490061	21 July, 2006

(1) **W:** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
(2) **R:** AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL
(3) **R:** AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL

21 June 2007 at 9:01 - ANSWER 9 OF 11

MEDLINE
2007280124-Full-text

Rationale, design and baseline data of a randomized, double-blind, controlled trial

comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS).

Diener Hans-Christoph; Sacco Ralph; Yusuf Salim

Department of Neurology, University Duisburg- EssenHufelandstrasse 55DE-45122 Essen, Germany. (Steering Committee; PRoFESS Study Group). h.diener@uni-essen.de

Journal

Cerebrovascular diseases (Basel, Switzerland), (2007) Vol. 23, No. 5-6, pp. 368-80. Electronic Publication: 2007-02-26.
Journal code: 9100851. ISSN: 1015-9770.

Language

English

Abstract

BACKGROUND: Individuals with **transient ischemic attack** and ischemic **stroke** have a high risk of recurrent **stroke** and death. While **acetylsalicylic acid (ASA, aspirin)** is proven and accepted as standard therapy in these patients, recent trials demonstrate that a combination of **ASA** and dipyridamole (DP) or clopidogrel may be superior to **ASA.** Blocking the renin-angiotensin system with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may also reduce recurrent **stroke.** The ongoing PRoFESS (Prevention Regimen for Effectively Avoiding Second **Strokes**) trial is designed to evaluate whether **ASA** + extended-release DP compared to clopidogrel, and whether **telmisartan** in addition to usual care in individuals after a **stroke**, will reduce the risk of further **strokes.** METHODS: PRoFESS is a multicenter, randomized, double-blind trial involving 695 sites from 35 countries or regions. Patients > or = 50 years presenting with an ischemic **stroke** < 120 days who were stable were randomized. The primary outcome for the trial is recurrent **stroke**, using a time-to-event analysis. The most important secondary outcome is the composite of **stroke**, myocardial infarction or vascular death. Other secondary outcomes include this composite + congestive heart failure, new-onset diabetes, other designated occlusive vascular events (pulmonary embolism, deep-vein thrombosis, peripheral arterial occlusion, **transient ischemic attack**, cerebral venous thrombosis or retinal vascular accident not classified as **stroke**), any death, **stroke** subtype by TOAST criteria and Mini Mental State Examination score. Safety is evaluated by assessing the risk of major hemorrhagic events. The comparison between **ASA** + DP and clopidogrel is based on an initial assessment of noninferiority, followed by evaluation of superiority, while for **telmisartan**, we will assess its superiority over placebo. RESULTS: With over 20,000 patients randomized, and utilizing a 2 x 2 factorial design, PRoFESS is the largest **stroke** trial to investigate the prevention of recurrent **stroke.** The mean age was 66.1 +/- 8.6 years, and 36.0% of the patients were females. The median time from qualifying event to randomization was 15 days with 39.9% of patients randomized within 10 days. According to the TOAST criteria, 28.5% of the **strokes** were due to large-vessel disease, 52.1% to small-vessel disease, 1.8% to cardioembolism, and 2.0% to other determined etiologies and 15.5% were of undetermined etiology. CONCLUSIONS: PRoFESS is the largest secondary **stroke** prevention trial to date and will directly compare two antiplatelet regimens as well as the benefit of **telmisartan** versus placebo.

MEDLINE
2003419797-Full-text

[Recurrence prophylaxis for stroke patients. Which platelet inhibitor combination protects best?]. Rezidivprophylaxe fur Schlaganfall-Patienten. Welche Plattchenhemmer-Kombination schutzt am besten?.

Anonymous

Journal

MMW Fortschritte der Medizin, (2003 Jul 24) Vol. 145, No. 29-30, pp. 63.
Journal code: 100893959. ISSN: 1438-3276.

Language

German

Effects of Aggrenox and telmisartan versus clopidogrel and aspirin in combinations on platelet activation and major receptor expression in diabetic patients: Relevance to the PRoFESS trial.

V. L. [Reprint Author] Serebruany; A. I. Malinin; W. Ziai; A. N. Pokov; M. J. Alberts; D. F. Hanley

Johns Hopkins Univ, Towson, MD USA

Journal

European Heart Journal, (AUG 2006) Vol. 27, No. Suppl. 1, pp. 233.
Meeting Info.: World Congress of Cardiology. Barcelona, SPAIN. September 02 -06, 2006.

Language

English ENTRY DATE: Entered STN: 10 Jan 2007 Last Updated on STN: 10 Jan 2007

The action of 2,6-bis[bis(2-hydroxyethyl)amino]-4,8- dipiperidinopyrimido[5,4-d] pyrimidine on the blood flow in experimental heart infarct and normal heart muscle

Manfred Kiese; Gerhard Lange; Klaus Resag

Univ. Marburg, Germany

Journal

Zeitschrift fuer die Gesamte Experimentelle Medizin (1960), 132, 426-35

Language

Unavailable

Abstract

cf. Arch. exptl. Pathol. Pharmakol. 231, 149(1957); 236, 225 (1959). The blood flow in normal dog heart was increased by intravenous injection of 0.03-2 mg./kg. of this compound (Persantin). Doses of 0.3-0.4 mg./kg. had approx. the same activity as 5 mg./kg. theophylline. Continuous infusion of the compound also stimulated circulation in myocardium after infarction. In heart-lung prepns. it increased O consumption of the isolated heart as much as 26%, which was associated with an improvement of heart output. But in the intact dog O utilization of the heart was not significantly increased even though blood flow rose 30-

75%.

21 June 2007 at 9:01 - ANSWER 3541 OF 3547 CAPLUS ©2007 ACS on STN
1960:82035-Full-text

The lactic and pyruvic acids and serum glutamic-oxalacetic and glutamic-pyruvic transaminases in cardiac cases treated with Persantin

E. Albach

Waldkrankenhaus, Berlin-Spandau

Journal

Medizinische Welt (1960) 993-6

Language

Unavailable

Abstract

Patients with decompensated cardiac insufficiency (blood lactic acid (I) 20-60 mg. %) showed a normal I (10-15 mg. %) only after 50 days of treatment with glucosides but gave normal I values in 12-21 days on the administration of 20-30 mg. Persantin/day. Pyruvic acid, and to a lesser extent, the transaminases also decreased (values not given). 39 references.

21 June 2007 at 9:01 - ANSWER 3542 OF 3547 CAPLUS ©2007 ACS on STN
1960:3145-Full-text

Relations between chemical structure and vasodilator action in pyrimido[5,4-d]pyrimidine derivatives

H. G. Menge; R. Kadatz

Univ. Cologne, Germany

Journal

Arzneimittel-Forschung (1959), 9, 476-80

Language

Unavailable

Abstract

The action of 12 pyrimido[4,5-d]pyrimidine derivs. on the blood flow in the coronary, muscular, and cerebral vessels of dogs has been studied. Action threshold of the most potent compds. was about 0.06 mg./kg. intravenously in coronary vessels, 0.5 mg. in. muscular, and 1-2 mg. in cerebral vessels. In cardiac and motor muscles only increase of blood flow was observed. Correlations between chemical structure and pharmacol. effect have been discussed in detail. In the most active compds. the basic structure was substituted both with hydrophilic hydroxyalkylamino groups and with lipophilic cyclic groups. The most marked and durable vasodilator action in cerebral and coronary vessels was observed in 2,6-bis[bis-(2-hydroxyethyl)amino]-4,8-dipiperidinopyrimido[5,4- d]pyrimidine.

21 June 2007 at 9:01 - ANSWER 3543 OF 3547 CAPLUS ©2007 ACS on STN

1959:67806-Full-text

Derivatives of pyrimido[5,4-d]pyrimidine

Patent Number GB 807826 21 January, 1959 GB

Dr. Karl Thomae, G. m. b. H. Chemisch-pharmaceutische Fabrik

Abstract

Almost all tetraminopyrimidopyrimidines (I) and most of their triamino and diamino derivs. are cardio-vascularly active compds. prepared from the corresponding chloro derivative of I and the corresponding amines. 4,6,8-Trichloropyrimidopyrimidine (4.7 g.) (m. 172°, obtained by refluxing the 4,6,8-trihydroxy derivative of I with PCl5 and POCl3) is introduced with cooling into 50 cc. MeOH-Na methylate solution (0.12 mole Na methylate), the mixture kept 6 hrs. at room temperature, neutralized with glacial AcOH, the precipitate removed by suction filtration and washed with H2O and Me2CO to yield 3.5 g. 4,6,8-trimethoxypyrimidopyrimidine, needles, m. 225-6° (sublimation from 200°) (MeOH). Also prepared from the tetrachloro derivative of I and the corresponding amines at room temperature are the following 2,6-dichloro-4,8-diaminopyrimidopyrimidines (4,8-di-substituent and m.p. given): N-hydroxyethylanilino, yellow prisms, 189-90° (MeOH); morpholino, 276-7°; p-chloranilino, 307-9° β-hydroxyethylamino, 246-8°; β-diethylaminoethylamino, 128-30°, methyldodecylamino, 76-7°; isoamylamino, 94-5°; benzylamino, 229-30°; p-dimethylaminoanilino, above 350°; diallylamino, 100-1°; methylcyclohexylamino, 179-81°; β-chlorethylamino, above 350°; butylethanolamino, 140-1° benzylethanolamino, 173-5°; 2,3-dihydroxypropylamino, 208-10°; amino, above 350°; carbethoxymethylamino, 207-9° (decomposition); and ethylthio, prisms, 190-2° (EtOH), prepared from 2,4,6,8-tetrachloropyrimidopyrimidine (II), m. 255-8° and Et mercaptan. 2,6-Dichloro-4,8- diiodopyrimidopyrimidine (III) is prepared by boiling II and NaI in Me2CO; III in dry dioxane treated with PhNH2 in absolute C6H6 yields 2,6-dichloro-4,8-dianilinopyrimidopyrimidine, m. 287-8° (dioxane). II (2.7 g.) and 45 g. PhNH2 refluxed 25 min. and the solution poured into 500 cc. 1N HCl yielded 4 g. 2,4,6,8-tetraanilinopyrimidopyrimidine, canary yellow needles, m. 300-2°. 6-Chloro-4,8- dimorpholinopyrimidopyrimidine (IV), needles, m. 199-200° is prepared from the corresponding 4,8-diiodo compound Also prepared are the following I (m.p. given): 6-morpholino-4,8-bis(diethylamino), ivory leaflets, 73-5° (MeOH-H2O); 6-methylamino-4,8-bis(ethylamino) 94-6°; 6-morpholino-4,8-di(ethylethanolamino), 120-2°; 6-anilino-4,8-diamino, 170-3°; 6-diethanolamino-4,8- bis(allylamino), 104-6°; 6-dimethylamino-4,8-diamino, 292-4°; 6-diethanolamino-4,8-dipiperidino, 100-5° (sintering from 95°); 6-(β-hydroxyethylamino)-4,8-dimorpholino, 106-8°; 6-methylethanolamino-4,8-bis(methylamino), 64-6°; 6-morpholino-4,8-di(γ-methoxypropylamino), 80-2°; 6-diisopropanolamino-4,8-dimorpholino, 106-8°; 6-diethanolamino-4,8-di(p-nitroanilino), 310-11°; 6-piperidino-4,8-di(β-hydroxyethylamino), 178-9°; 6-diethanolamino-4,8-dimorpholino, 150-2°; 6-morpholino-4,8- bis(ethylamino), 151-3°; 6-morpholino-4,8-diamino, 266-7°; 2,6-dimorpholino-4,8-di(β-propoxyethoxy), yellow powder, 122-4° (MeOH-H2O); 2,6-bis(β-diethylaminoethoxy)-4,8- bis(diethylamino), 35.5-7°; 6-chloro-2-thio-4,8-dimorpholino, yellow, 240° (glacial AcOH); 6-chloro-2-thio-4,8-dipiperidino, orange, 242-3° (BuOH); 6-methylthio-2,4-dimorpholino, yellow, 130-2° (MeOH), prepd from 6-methylthio-2,4- dichloropyrimidopyrimidine, 100-3°; 2,6-diethoxy-4,8-bis(β- diethylamino-ethylamino), needles, 78-8.5° (dilute HCl and petr. ether); 2,6-dimorpholino-4,8-diethylthio, orange prisms, 293-5° (HCONMe2); 6-morpholino-4,8-di(carboxymethylthio), yellow, 241-2° (dilute NH3); 6-carboxymethylthio-4,8-dipropylamino, brown prisms, 172-4° (MeOH), prepared with thioglycollic acid in the presence of pyridine; 2,6-bis(diethanolamino)-4,8-dipiperidino, yellow needles, m. 162-3° (EtOAc); 2,6-bis(diethanolamino)-4,8-bis(diethylamino), 167-8°; 2,6-bis(diethanolamino)-4,8-dipyrrolidino, 186-7°; 2,6-bis(diethanolamino)-4,8-bis(diallylamino), 110°; 2,6-bis(diethanolamino)-4,8-bis(di-methylamino), 182-3°; 2,6-bis(diethanolamino)-4,8-bis(dibutylamino), 124-6°; 2,6-di(methylethanolamino)-4,8-dipiperidino, 122-4°; (sintering from 114°); 2,6-di(propylethanolamino)-4,8-dimorpholino, 138-9°; 2,6-bis(diisopropanolamino)-4,8-dipiperidino, 182-3°; 2,6-di(methylethanolamino)-4,8-di(dodecylethanolamino), 88-90°; 2,6-bis(diethanolamino)-4,8-dimorpholino, 202-4°; 2,6-dimorpholino-4,8-di(ethylethanolamino), yellow needles, 190-1°; 2,6-dimorpholino-4,8-di(propylethanolamino), 141-3°; 2,6-dimorpholino-4,8-di(methylethanolamino), 207-9°; 2,6-dimorpholino-4,8-bis(diethanolamino), 209-10°; 2,6-dipiperidino-4,8-bis(diethanolamino), 182-4°; 2,6-bis(diethylamino)-4,8-bis(diethanolamino), 158-60°; 2,6-dimorpholino-4,8-bis-(dimethylamino), 192-3°; 2,6-dipiperidino-4,8-bis(isoamylamino), 192-4°; 2,6-dipiperidino-4,8-dipyrrolidino, 254-6°; and 2,6-dipiperidino-4,8-di(benzylethanolamino), 161-3°. II (2.7 g.) is stirred in small portions into 50 cc. absolute alc.-Me2NH solution (0.14 mole), the obtained dichlorodiamino compound and 0.1 g. CuSO4 heated 1 hr. to 200° in a bomb-tube and diluted with H2O, the separated product dissolved in 200 cc. O.2N HCl, treated with animal C, and precipitated with concentrated NH3 to give 1.7 g. 2,4,6,8-tetra(dimethylamino)pyrimidopyrimidine, yellow needles, m. 164-5° (recrystd. 3 times from absolute alc. and dried at 130° and 0.1 Torr.). Similarly prepared are 2,4,6,8-tetramino derivs. of I, the tetra substituent and m.p. given: allylamino, 201-2°; methylethanolamino, 155-6°; β-hydroxyethylamino, 180-2°; piperidino, 163-5°; morpholino, 266-8°; p-chloranilino, over 330°; amino, over 350°; methylamino, 202-4°; phenoxy, leaflets, 289-90° (C6H6 and HCONMe2); phenylthio, yellow prisms, 240-4° (HCONMe2) (from thiophenol);

thio, carmine-red, above 350° (HCONMe2) (from Na hydrosulfide); ethylthio, brownish yellow prisms, 140-1°; (EtOH) (from Et mercaptan in the presence of C5H5N). Similarly, 4,6,8-triamino derivs. of I, the tri-substituent an m.p. given: methylamino, 188-9° (H2O), a diuretic; ethylamino, 83-5°; propylamino, 84-6°; dimethylamino, 92-3°; β-hydroxyethylamino, 83-5°; morpholino, 182-4°; anilino, 203-4°; p-chloro-anilino, 274-5°; o-methoxyanilino, 214-15°; and carboxymethylthio, yellow needles, 230-1° (dark coloration towards 190°) (dilute NH3) (from thioglycollic acid in the presence of C5H5N). Prepared from IV and the corresponding Na alcoholate solns. are 6-alkoxy-4,8-dimorpholino derivs. of I, and 6-substituent and m.p. given: ethoxy, 129-32° (EtOH); butoxy, 109-11°; β-diethylaminoethoxy, 100-3°, a diuretic; β-ethoxyethoxy, 111-12°; and β-propoxyethoxy, 122-3°. Prepared from 4,6,8-trichloro derivs. of I at room temperature are 6-chloro-4,8-diamino derivs. of I, (the 4,8-disubstituent and m.p. given): allylamino, needles, 114-16° (EtOH); methylethanolamino, 90-2°; diisopropanolamino, 177-9°; methylamino, 227-9°; diethanolamino, 135-6°; p-nitroanilino, above 350°; 3-methoxypropylamino, 98-100°; o-methoxyanilino, 290-2°; dibenzylamino, 160-3°; ethyleneimino, from 130°, yellow coloration and decomposition at approx. 170 °; and semicarbazido, above 360°. Prepared from 4,8-dichloro derivative of I are the following 4,8-diamino derivs. of I (the 4,8-disubstituent and m.p. given): morpholino, prisms, 197-8° (C6H6); piperidino, scales, 132-4° (MeOH); anilino, yellow needles, m. 257-8° (HCONMe2); amino, needles, above 260° (dilute HCl); methylamino, 265° (H2O); dimethylamino, needles, 115° (H2O); hydrazino, m. 226° (dilute HCl); N, N'-diphenylguanidino, yellow, 245° (sinters at 200°) (dilute HCl); β-hydroxyethylamino, 204-5° (MeOH); N-hydroxy-p-nitroanilino, yellow, 265-7° (HCONMe2); and thio, orange, above 350° (dilute NH3).

Language

Unavailable

Application Information

GB 1956-8017 14 March, 1956

Patent Information

Number	Kind	Date	Application	Date
GB 807826		21 January, 1959	GB 1956-8017	14 March, 1956

1959:64143-Full-text

Circulatory and clinical studies on 2,6-bis[bis(2-hydroxyethyl)amino] -4,8-dipiperidinopyrimido[5,4 - d]pyrimidine

Herbert Spitzbarth

Univ. Mainz, Germany

Journal

Arzneimittel-Forschung (1959), 9, 59-63

Language

Unavailable

Abstract

cf. preceding abstrs. Intravenous injection of 40-80 mg. in normal humans resulted in 10-15 mm. lowering of systolic and diastolic blood pressure within 2 min. accompanied by reddening of the face, feeling of warmth, and increased pulse. Similar effects were obtained with oral doses of 50-40 mg. In patients with labile hypertension the blood pressure drop was more apparent and reduction of stroke volume and cardiac output were observed.

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1959:64141-Full-text

The cardiac and circulatory action of 2,6-bis[bis(2-hydroxyethyl)amino] -4,8-dipiperidinopyrimido[5,4 - d]pyrimidine

Th. Hockerts; G. Bogelmann

Univ. Wurzburg, Germany

Journal

Arzneimittel-Forschung (1959), 9, 47-9

Language

Unavailable

Abstract

cf. preceding and following abstrs. In dogs kept under O respiration, 0.5 mg./kg. of the title compound caused excessive increase of coronary blood flow, with slight lowering of blood pressure. No marked influence on heart rate and on cardiac performance was observed.

 CAPLUS ©2007 ACS on STN
1959:64139-Full-text

Pharmacological properties of a new coronary dilator, 2,6-bis[bis(2-hydroxyethyl)amino] -4,8- dipiperidinopyrimido[5,4-d]pyrimidine

R. Kadatz

Dr. Karl Thomae G. m. b. H., Biberach/Riss, Germany

Journal

Arzneimittel-Forschung (1959), 9, 39-45

Language

Unavailable

Abstract

The title compound (I) forms intense yellow crystals of bitter taste, m. 163°, sparingly soluble in H2O, easily soluble in dilute acids, MeOH, and EtOH, sparingly soluble in Me2CO, AcOEt, benzene. The solns. are yellow with strong blue-green fluorescence. The acute L.D.50 in the white mouse is 0.15 g./kg. intravenous, 2.7 g. subcutaneous, and 2.15 g. oral. Intracoronary injection of 0.3 mg./kg./min. increases coronary blood flow of dogs by 113%. The effect of I is more than double that of papaverine. Coronary vessels are dilated by I without marked influence on the blood pressure. I does not increase O consumption of isolated guinea pig heart prepns. in concns. up to 10-5. It shows spasmolytic effect in the isolated intestine contracted by BaCl2, and on histamine and acetylcholine bronchospasm. The action of I is mainly peripheral. It causes increased coronary blood flow with marked and persisting coronary dilatation without affecting blood pressure, heartbeat frequency, myocardial O consumption, and heart action. Cf. following abstrs.

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1939:58164-Full-text

Phytochemistry of the bark of Tabernaemontana coronaria Br

A. N. Ratnagiriswaran; K. Venkatachalam

Journal

Quarterly Journal of Pharmacy and Pharmacology (1939),
12, 174-81

Language

Unavailable

Abstract

The bark of the stem and root of this plant contains the following constituents: fatty matter yielding on saponification palmitic, cerotic and oleic acids, a crystalline substance m. 180-1° with properties resembling those of a resin alc., caoutchouc, resins, sugars, KNO3, KCl and alkaloids. Two alkaloids, named tabernaemontanine and coronarine, have been isolated in the pure state. Results of micro-analyses indicate the formula C20H26N2O3 for the former and C44H56N4O6 for the latter alkaloid. Preliminary expts. show that the alkaloids are pharmacologically active.

1980:20278-Full-text

Cyclic nucleotide phosphodiesterase of normal and leukemic lymphocytes. Kinetic properties and selective alteration of the activity of the multiple molecular forms

William N. Hait; Benjamin Weiss

Dep. Pharmacol., Med. Coll. Pennsylvania, Philadelphia, PA, 19129, USA

Journal

Molecular Pharmacology (1979), 16(3), 851-64

Language

English

Abstract

The multiple forms of cyclic AMP phosphodiesterase (I) and GMP phosphodiesterase (II) of normal and leukemic lymphocytes were separated by gel electrophoresis and characterized by kinetic properties and response to activators and inhibitors. The patterns of the I of normal and leukemic cells were similar: both had 4 forms of enzyme, designated as I, IA, III, and IV. Peaks I, IA, and IV had standard Michaelis-Menten kinetics with apparent Km values of 10, 10, and 70 μm resp. Peak III, a major form of I activity, had anomalous kinetic behavior, suggestive of an allosteric enzyme with pos. cooperativity. The pattern of the II of leukemic lymphocytes was different from that of the normal lymphocytes. Normal lymphocytes had 3 forms of II corresponding to peaks IA, III, and IV of I. However, leukemic lymphocytes showed only 2 forms of II; these corresponded to peaks III and IV of I. The apparent Km values for peak III (the major peak) was similar in the 2 types of cells (100 μM). Peak IV showed Km values of 10 μM for normal lymphocytes and 40 μM for leukemic lymphocytes. Peak IA was present only in normal lymphocytes and had an apparent Km of 16 μM. A study of the I activities of mouse cerebrum and salivary gland showed that the major form of phosphodiesterase in these tissues did not correspond to that found in leukemic lymphocytes. Calmodulin increased the activity of the major form of phosphodiesterase isolated from cerebrum but had no effect on the forms of phosphodiesterase isolated from lymphocytes of several other tissues. Cyclic GMP (5 μM) increased the activity of the major form of I from normal and leukemic lymphocytes but had no effect on other forms of phosphodiesterase of lymphocytes. This

selective activation by GMP of the phosphodiesterase of lymphocytes normalized the anomalous kinetic behavior of this form of the enzyme. The various forms of phosphodiesterase from leukemic lymphocytes and normal tissues of the mouse were selectively activated and inhibited by drugs. Since an abnormal metabolism of cyclic nucleotides may be associated with malignancy, the data suggest the possibility of developing chemotherapeutic agents that act by selectively altering the metabolism of cyclic nucleotides in malignant tissue.

21 June 2007 at 9:01 - ANSWER 201 OF 212 CAPLUS ©2007 ACS on STN
1980:806-Full-text

Prostacyclin (PGI2) and the effect of phosphodiesterase inhibitors on platelet aggregation

Kaj Anker Joergensen; Joern Dyerberg; Erik Stoffersen

Coagulation Lab., Aalborg Hosp., Aalborg, DK-9100, Den.

Journal

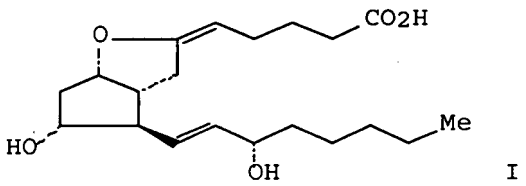
Pharmacological Research Communications (1979), 11(7), 605-15

Language

English

Abstract

The effect of PGI2 (I) [35121-78-9] on thrombin-induced aggregation of washed, acetylated human platelets was greatly prolonged by the **phosphodiesterase inhibitors** theophylline [58-55-9] and dipyridamole [**58-32-2**]. A potentiating effect was also demonstrated. Since the **phosphodiesterase inhibitors** prolong the inhibitory effect of I on platelet aggregation, they may be useful in conjunction with I in the treatment of thromboembolic diseases.



I

21 June 2007 at 9:01 - ANSWER 202 OF 212 CAPLUS ©2007 ACS on STN
1979:197437-Full-text

Effect of theophylline and other drugs on rabbit renal cyclic nucleotide phosphodiesterase, 5'-nucleotidase and adenosine deaminase

Bertil B. Fredholm; Per Hedqvist; Louise Vernet

Dep. Pharmacol., Karolinska Inst., Stockholm, Swed.

Journal

Biochemical Pharmacology (1978), 27(24), 2845-50

Language

English

Abstract

In homogenates of rabbit renal cortex and medulla, theophylline (I) [58-55-9] was a competitive **inhibitor** of cyclic nucleotide **phosphodiesterase** [9040-59-9] and a noncompetitive **inhibitor** of alkaline phosphatase [9001-78-9] and 5'-nucleotidase (EC 3.1.3.5) (II) [9027-73-0], but did not affect adenosine deaminase (EC 3.4.5.4) [9026-93-1]. Cyclic AMP [60-92-4] and cyclic GMP [7665-99-8] hydrolysis were inhibited to an equal extent by I, furosemide (III) [54-31-9], and caffeine [58-08-2], but dipyridamol [**58-32-2**] and other drugs inhibited cyclic AMP hydrolysis in concns. at least 10 times lower than those required to inhibit cyclic GMP hydrolysis, whereas dilazep [35898-87-4] and 2-O-propoxyphenyl-8-azapurin-6-one [37762-06-4] were more potent as cyclic GMP hydrolysis inhibitors. I, III, ethacrynic acid [58-54-8], chlorthalidone [77-36-1], and cyclopenthiazide [742-20-1] inhibited II at concns. ≤1mM. Of the drugs tested at 1mM concentration, only dipyridamol and chlorthalidone inhibited adenosine deaminase activity significantly.

CAPLUS ©2007 ACS on STN
1979:109967-Full-text

Pharmaceutical preparation for hindering thrombocyte aggregation

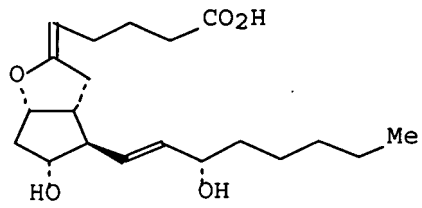
Patent Number DE 2821737 A1 30 November, 1978

Wellcome Foundation Ltd., UK

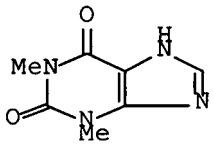
Ger. Offen., 29 pp.

Abstract

The action of prostacyclin (I) [35121-78-9] and its derivs., which inhibits blood platelet aggregation and is useful for prevention and treatment of thrombosis, is potentiated by **phosphodiesterase** [9025-82-5] **inhibitors.** The vasodilatory action of I and its derivs., which is undesirable e.g., in treatment of heart infarct or in extracorporeal circulation, is not potentiated by **phosphodiesterase inhibitors** and may thus be diminished by addition of these compds. For example, infusion into the thrombotic carotid artery of rabbits of a combination of I (subthreshold dose of 25 ng/kg/min) and theophylline (II) [58-55-9] (125 μg/kg/min) resulted in disappearance of these thrombi.



I



II

Language

German

Inventor(s)

Cuatrecasas, Pedro; Moncada, Salvador

Application Information

DE 1978-2821737 18 May, 1978

Priority Information

US 1977-799007 A 20 May, 1977
GB 1977-35261 A 23 August, 1977
US 1978-907355 A3 18 May, 1978

Patent Information

Number	Kind	Date	Application	Date
DE 2821737	A1	30 November, 1978	DE 1978-2821737	18 May, 1978
DE 2821737	C2	19 May, 1988		
SE 7805707	A	21 November, 1978	SE 1978-5707	18 May, 1978
SE 443716	B	10 March, 1986		
SE 443716	C	19 June, 1986		
NL 7805402	A	22 November, 1978	NL 1978-5402	18 May, 1978
FR 2390964	A1	15 December, 1978	FR 1978-14729	18 May, 1978
FR 2390964	B1	11 July, 1980		
JP 54002335	A	9 January, 1979	JP 1978-59460	18 May, 1978
US 4337254	A	29 June, 1982	US 1978-907355	18 May, 1978
HU 22858	A2	28 July, 1982	HU 1978-WE576	18 May, 1978
HU 180548	B	28 March, 1983		
CH 643458	A5	15 June, 1984	CH 1978-5416	18 May, 1978
GB 1601034	A	21 October, 1981	GB 1978-20694	19 May, 1978
US 4404212	A	13 September, 1983	US 1981-280263	2 July, 1981
US 4393063	A	12 July, 1983	US 1981-280853	6 July, 1981

1978:590986-Full-text

Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiating endogenous prostacyclin

S. Moncada; R. Korbut

Dep. Prostaglandin Res., Wellcome Res. Lab., Beckenham, UK

Journal

Lancet (1978), 1(8077), 1286-9

Language

English

Abstract

The antithrombotic effect of dipyridamole (I) [58-32-2] (1, 5, 10, or 50 μg/mL for 3 min), when infused into blood superfusing rabbit tendons, was due to phosphodiesterase [9025-82-5] inhibition and depended on stimulation of platelet cyclic AMP by circulating prostacyclin (II) [35121-78-9] in the blood. Low doses of aspirin [50-78-2] (5 or 10 mg/kg, i.v.) potentiated the antithrombotic effects of I and theophylline [58-55-9] (5 mg/kg, i.v.) by inhibiting platelet cyclooxygenase. High doses of aspirin (150 mg/kg, i.v.) prevented II formation, thus abolishing the antithrombotic effects of I. Therefore, the antithrombotic effectiveness of the combination of aspirin and I depended critical on the doses used.

21 June 2007 at 9:01 - ANSWER 205 OF 212 CAPLUS ©2007 ACS on STN
1977:599025-Full-text

Modulation of human leukocyte migration inhibitory factor (LIF) by 3',5'-cyclic AMP, 3', 5'-cyclic GMP and agents known to influence intracellular cyclic nucleotide metabolism

K. Bendtzen; J. Palit

Med. Dep. TA, Rigshosp. Univ. Hosp., Copenhagen, Den.

Journal

Acta Pathologica et Microbiologica Scandinavica,
Section C: Immunology (1977), 85C(5), 317-23

Language

English

Abstract

The effects of 3',5'-cyclic AMP (cAMP), 3',5'-cyclic GMP (cGMP) and their dibutyryl derivs., and the effects of various both cyclic and noncyclic nucleotides and of nucleosides on the in vitro migration of human peripheral blood leukocytes under agarose and on the activity of leukocyte migration inhibitory factor (LIF) was studied. Leukocyte migration was not significantly influenced by any of the above-mentioned drugs. However, LIF activity was significantly depressed by cAMP and dibutyryl cAMP, whereas cells challenged with 10-4M of the other drugs, including 2',3'-cyclic AMP, 3'-AMP, 5'-AMP and adenosine, showed unreduced migration inhibition under standard test condtions. A possible role of cAMP in the mechanism of LIF action was supported further by expts. with various drugs known to influence intracellular cAMP metabolism Treatment of leukocytes with cAMP generating, β-adrenergic agent isoproterenol (10-4M) caused a rapid, transient reduction of LIF activity as compared to LIF-treated controls. The α-adrenergic agent norepinephrine (10-4M) was ineffective. Treatment of leukocytes with the **phosphodiesterase inhibitors** papaverine (10-4M) and dipyridamole (2 + 10-5) enhanced their motility and enabled them to escape migration inhibition as compared to LIF-treated controls. The cGMP may also participate in the expression of LIF activity, since cells treated with cGMP partially escaped migration inhibition during the first 3 h of migration.

21 June 2007 at 9:01 - ANSWER 206 OF 212 CAPLUS ©2007 ACS on STN
1977:462421-Full-text

Selective inhibition of separated forms of human platelet cyclic nucleotide phosphodiesterase by platelet aggregation inhibitors

Tomiko Asano; Yasuo Ochiai; Hiroyoshi Hidaka

Dep. Biochem., Inst. Dev., Kasugai, Japan

Journal

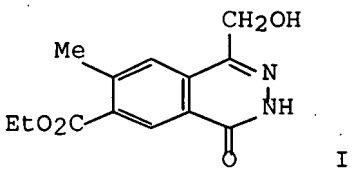
Molecular Pharmacology (1977), 13(3), 400-6

Language

English

Abstract

Human platelets contain 3 distinct cyclic nucleotide phosphodiesterase, a relatively specific cyclic GMP phosphodiesterase (F 1) [9068-52-4], a cyclic nucleotide phosphodiesterase (F II) [9040-59-9], and a relatively specific cyclic AMP phosphodiesterase (F III) [9036-21-9]. The possibility of selective inhibition of these 3 forms of the **phosphodiesterase** by various platelet aggregation **inhibitors**: papaverine [58-74-2], theophylline [58-55-9], caffeine [58-08-2], EG 626 (I) [56611-65-5], adenosine [58-61-7], 2-chloroadenosine [146-77-0], and dipyridamole [**58-32-2**] was studied. Selective inhibition was found when the inhibitory potencies of the compds. were compared by means of Dixon plots. All agents tested except dipyridamole showed relatively selective inhibition for F III, and the order of potency of these drugs as inhibitors of the F III enzymes was papaverine, I, dipyridamole, theophylline, 2-chloroadenosine, caffeine, and adenosine. I was 30 times more potent as an inhibitor of F III than of F I. On the other hand, dipyridamole was 20 times more potent as an inhibitor of F I than of F III. The Di values of these agents for F I and F III were identical whether cyclic AMP [60-92-4] or cyclic GMP [7665-99-8] was used as a substrate. However, these compds. revealed approx. 2 times more affinity for F II using cyclic GMP than with cyclic AMP as substrate. The Ki values of these compds. for inhibition of cyclic AMP hydrolysis by F II decreased by half in the presence of 2 μM cyclic GMP and were found to correspond to the Ki values obtained using cyclic GMP as substrate. Hydrolysis of cyclic AMP by F II was stimulated by 0.1-10 μM cyclic GMP. The decreased Ki values in the presence of a low concentration of cyclic GMP may be due to the effect of cyclic GMP on the active site of F II.



I

1976:516710-Full-text

Effect of some phosphodiesterase inhibitors on central dopamine mechanisms

Bertil B. Fredholm; Kjell Fuxe; Luigi Agnati

Dep. Pharmacol., Karolinska Inst., Stockholm, Swed.

Journal

European Journal of Pharmacology (1976), 38(1), 31-8

Language

English

Abstract

The effect of five **phosphodiesterase** (PDE) **inhibitors**, (papaverine [58-74-2], 3-isobutyl-1-methylxanthine (IBMX) [28822-58-4], theophyllamine [317-34-0], dipyridamol [**58-32-2**] and M and B 22,948 [37762-06-4]) was studied on adenylate cyclase [9012-42-4] and on cyclic nucleotide phosphodiesterase activities in exts. of rat caudate nucleus. For comparison the effect on dopamine (DA) [51-61-6] turnover and on turning behavior in rats with unilateral lesions of the nigro-neostriatal DA neutrons was studied. Cyclic AMP phosphodiesterase [9036-21-9] was inhibited by papaverine, dipyridamol, IBMX, M and B 22,948

and theophyllamine in that order of potency. Cyclic GMP phosphodiesterase [9068-52-4] was inhibited by IBMX, papaverine, M and B 22,948 and theophyllamine, but not by dipyridamol. Basal adenylate cyclase was higher if assayed in the presence of papaverine or dipyridamol than if theophyllamine or IBMX was present. The degree of stimulation caused by DA was not significantly influenced by the PDE inhibitors. Papaverine and dipyridamol enhanced DA disappearance in the caudate nucleus and the tuberculum accumbens, but not in the median eminence. Caffeine [58-08-2] had no significant effect. Papaverine (1-25 mg/kg) had no significant effect on L-dopa [59-92-7] (5 mg/kg)-induced turning, and actually inhibited turning induced by combination of L-dopa (10 mg/kg) and atropine [51-55-8] (5 mg/kg). The other four PDE inhibitors all potentiated L-dopa-induced turning. Theophyllamine (20 mg/kg) and IBMX (5 mg/kg) even caused turning when given alone. Thus, PDE inhibition leads to enhanced effect of DA in the caudate nucleus. However, the results also demonstrate that several of the PDE inhibitors have effects on central DA mechanisms that are difficult to explain solely on the basis of PDE inhibition.

21 June 2007 at 9:01 - ANSWER 208 OF 212 CAPLUS ©2007 ACS on STN
1976:99197-Full-text

The effect of non-steroid anti-inflammatory drugs, dibutyryl cyclic 3',5'-adenosine monophosphate and phosphodiesterase inhibitors on platelet aggregation and the platelet release reaction in normal and essential fatty acid deficient rats

J. E. Vincent; F. J. Zijlstra; I. L. Bonta

Med. Fac., Erasmus Univ., Rotterdam, Neth.

Journal

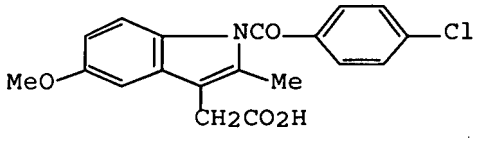
Prostaglandins (1975), 10(5), 899-911

Language

English

Abstract

A comparison was made of the action of 3 classes of substances with platelet aggregation inhibiting effect in normal and essential fatty acid deficient rats. In the latter group, the effect of indomethacin (I) [53-86-1] (0.6-1.8 mM) was considerably reduced, whereas the difference was smaller with aspirin [50-78-2] (22.5-67.5 mM). Dibutyryl cyclic AMP [362-74-3] (5 mM) had the same inhibiting effect in both groups. Of the **phosphodiesterase inhibitors** tested, dipyridamole [**58-32-2**] (10-3M) was inactive, whereas the inhibiting effects of caffeine [58-08-2] (10 mM) and papaverine [58-74-2] (0.5 mM) were slightly reduced in the deficient animals. The same differences between the 2 groups were seen in the magnitude of the release reaction after 14C-serotonin labeling. These data support the idea that the non-steroid anti-inflammatory drugs act by inhibiting the formation of an aggregation-inducing substance from arachidonic acid.



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21 June 2007 at 9:01 - ANSWER 209 OF 212 CAPLUS ©2007 ACS on STN
1976:99173-Full-text

Relative potencies of dipyridamole and related agents as inhibitors of cyclic nucleotide phosphodiesterases. Possible explanation of mechanism of inhibition of platelet function

Frances A. McElroy; Richard B. Philp

Dep. Pharmacol., Univ. West. Ontario, London, ON, Can.

Journal

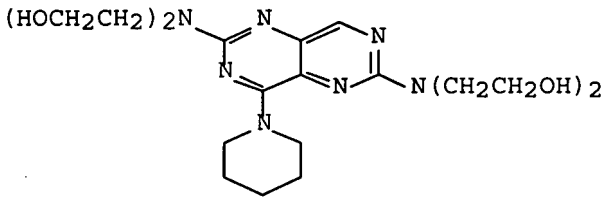
Life Sciences (1975), 17(9), 1479-93

Language

English

Abstract

Effects of dipyridamole [58-32-2] and 5 related agents (RA233 (I) [13665-88-8], RA255 [13665-55-9], RA433 [13665-58-2], VK744 [31895-42-8], and VK774 [33548-44-6]) on several aspects of human platelet cyclic nucleotide metabolism were investigated. In platelet-rich plasma VK774 caused a significant increase in total cyclic AMP [60-92-4] and a potentiation of adenosine [58-61-7]-induced cyclic AMP accumulation. VK774 and I potentiated the adenosine effect while dipyridamole caused a lowering of cyclic AMP levels both in the absence and presence of adenosine. All 6 agents inhibited the cyclic AMP phosphodiesterase [9036-21-9] of collagen-treated platelets, the high affinity cyclic AMP phosphodiesterase of platelet lysates, and the cyclic GMP phosphodiesterase [9068-52-4] of membrane-enriched platelet fractions. Ki values for these agents were determined for both the high affinity cyclic AMP and cyclic GMP phosphodiesterases. The order of potency of these drugs as inhibitors differed for the 2 enzymes studied. Neither order showed a clearcut relationship to the reported relative potencies of the drugs in inhibiting a number of other aspects of platelet function. If the relative selectivity of these agents for the 2 enzymes was however determined, there was a close correspondence between their tendency to promote a relative accumulation of cyclic AMP and their inhibitory effects on platelet adhesion and aggregation. This close correspondence was taken to indicate that these drugs exert many of their effects on platelet function by altering the relative Cyclic nucleotide levels and, moreover, supports the contention that platelet aggregation and release are modulated by both cyclic AMP and cyclic GMP.



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1975:106437-Full-text

Effects of catechol amines, cyclic nucleotides, and phosphodiesterase inhibitors on contractions of skeletal muscles in anesthetized cats

W. C. Bowman; M. W. Nott

Dep. Physiol. Pharmacol., Univ. Strathclyde, Glasgow, UK

Journal

Clinical and Experimental Pharmacology and Physiology
(1974), 1(4), 309-23

Language

English

Abstract

The cyclic nucleotide **phosphodiesterase inhibitors** ICI 63197 (I) [33406-42-7], ICI 58301 [23280-04-8], papaverine [58-74-2] , theophylline [58-55-9], and dipyridamole [**58-32-2**], in decreasing order of potency, potentiated the depressant effect of (-)-isoprenaline bitartrate [59-60-9] on tension and fusion of incomplete tetanic contractions of the slow-contracting soleus muscle of cats when given i.v. I potentiated isoprenaline in its enhancing effect on tension and degree of fusion of incomplete tetanic contractions of the fast-contracting tibialis anterior and flexor digitorum longus muscles. However, cyclic AMP itself and its dibutyryl analog, injected intraarterially, did not consistently affect muscle contractility. High doses of the **phosphodiesterase inhibitors** (except theophylline) alone produced isoprenaline-like effects on the soleus muscle, which were partially antagonized by (+)-propranolol-HCl [13071-11-9] or sotalol [3930-20-9]; the antagonism was independent of β-adrenoceptor blockade. The effects of sympathomimetic amines on muscle contractility may be mediated by 3',5'-cyclic AMP [60-92-4].

For diagram(s), see printed CA Issue.

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1973:67018-Full-text

Effects of some phosphodiesterase inhibitors on the conductance of the perfused vascular beds of the chloralosed cat

T. C. Hamilton

Pharmacol. Dep., Roche Prod. Ltd., Welwyn Garden City, UK

Journal

British Journal of Pharmacology (1972), 46(3), 386-94

Language

English

Abstract

In chloralosed cats, theophylline [58-55-9], dipyridamole [**58-32-2**] and 4-(3,4-dimethoxybenzyl)-2-imidazolidinone(Ro 7-2956)(I) [26772-42-9] and its analogs such as Ro 20-0419 [34127-90-7] Ro 20-1724 [29925-17-5], and Ro 20-3760 [38473-22-2] were more potent vasodilators in the splachnic region than in the hindquarters, whereas papaverine [58-74-2] was a potent vasodilator in both of these vascular beds. The vasodilator response to these **phosphodiesterase inhibitors** in the splanchnic region and hindquarters was not susceptible to β-adrenoceptor blockade. Infusion of dibutyryl cyclic AMP [362-74-3] into the superior mesenteric artery increased vascular conductance of the splanchnic region, and this effect was enhanced by Ro 20-1724 in doses below those in which this compound affected conductance. The accumulation of cyclic AMP [60-92-4] in vascular smooth muscle may mediate the vasodilator response to **phosphodiesterase inhibitors.**

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1972:496757-Full-text

Activation and inhibition of lipolysis in isolated fat cells by various inhibitors of cyclic AMP phosphodiesterase

U. Schwabe; S. Berndt; R. Ebert

Inst. Pharmakol., Med. Hochsch. Hannover, Hanover, Fed. Rep. Ger.

Journal

Naunyn-Schmiedeberg's Archives of Pharmacology (1972),
273(1-2), 62-74

Language

English

Abstract

Lipolysis in isolated fat cells of rat epididymal adipose tissue was stimulated by theophylline (I) [58-55-9] and caffeine (II) [58-08-2] and not affected by papaverine (III) [58-74-2], dipyridamole (IV) [**58-32-2**], or imipramine (V) [50-49-7]. I potentiated noradrenaline-induced lipolysis. III, IV, and V inhibited lipolysis induced by noradrenaline, I, or dibutyryl cyclic AMP. I, III, IV, and V competitively inhibited both types (different Michaelis consts.) of cyclic AMP phosphodiesterase [9036-21-9] in rat adipose tissue. A possible mechanism for the antilipolytic effect of the **phosphodiesterase inhibitors** is discussed.